PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 203/04, A61K 31/21, C07D 333/22, 209/46, 491/04, A61K 31/40, 31/38, C07D 207/337, 209/88, 333/24, A61K 31/16, C07C 235/78, 235/34, 233/21

A1

(11) International Publication Number: WO 94/12463

(43) International Publication Date: 9 June 1994 (09.06.94)

(21) International Application Number: PCT/EP93/03193

(22) International Filing Date: 15 November 1993 (15.11.93)

(30) Priority Data:
MI92A002699 26 November 1992 (26.11.92) IT

(71) Applicant *(for all designated States except US)*: HCT-HEALTH CARE TRADING LTD. [IE/IE]; Dame Street, Dublin 2 (IE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ARENA, Barbara [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agent: TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I-20133 Milano (IT).

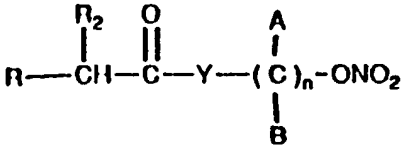
(81) Designated States: AU, BR, CA, CZ, FI, HU, JP, KP, KR, NO, NZ, PL, RO, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

(57) Abstract

Nitric esters with pharmacological activity having general formula (I), their pharmaceutical utilisation and process for their preparation.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

Object of the present invention are nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity, their pharmaceutical utilization and the process for their preparation.

PRIOR ART

Some derivatives of propionic acid, such as for instance 2-(-3-benzoylphenyl)propionic acid, commonly known as ketoprofen, have been used for a long time as pharmaceutical preparations for their anti-inflammatory activity and are sold on the different international markets since many years. The process for the preparation of 2-(3-benzoylphenyl)propionic acid has been described in the South African patent n° 68 00,524, corresponding to the US patent 3,641,127; in the French patent n° M6444 and also in C.A. 75,5528m (1971); G.A. PINNA et al., FARMACO Ed. Sci. 35,684 (1980); while the pharmacokinetics in humans is described in T. ISHIZAKI et al., Eur.J.Clin. Pharmacol. 18,407 (1980). The use of derivatives of propionic acid, such as, for instance, keptofren, as well as the use of other products which are utilized as anti-inflammatory agents, involves, as known, severe adverse reactions, for instance in the gastrointestinal apparatus, as well as possible damages to the liver and the kidneys.

There is much experimental evidence [S. MONCADA, R.M.J.PALMER, E.A.HIGGS, Pharmacological Reviews,

43(2), 109 (1991); T.H.LUSHER, C.M.BOULANGER, Y.DOHI, Z.YANG, Hypertension, 19,117 (1992)], on whose basis the integrity of vasal endothelium is thought to be a basic barrier against the onset of pathological processes in several organs and apparatuses.

Such protection barrier, and therefore the integrity of the vasal endothelium, is ensured physiologically by the presence of nitric oxide and prostacyclin.

The treatment with non steroid drugs having an anti-inflammatory activity, such as, for instance, 2-(3-benzoylphenyl)propionic acid or ketoprofen, causes the inhibition of cyclo-oxygenase, an enzyme which syntesizes the precursor of prostacyclin.

As a consequence, having so inhibited the production of prostacyclin, the reserve of same in the tissues is markedly depauperated, and therefore the integrity of vasal endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological process break out which affect the gastrointestinal apparatus, liver and kidneys.

OBJECTS OF THE INVENTION

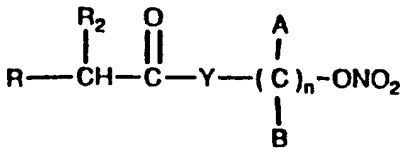
Object of the present invention is that to provide a group of products which, while ensuring the maintenance of the pharmacological activity characteristic of the known anti-inflammatory agents, are capable of eliminating the adverse reactions caused by the treatment with

said agents.

Another object of the present invention is the realization of a process for the preparation of a group of products having an anti-inflammatory activity while being exempt from the adverse reations which are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

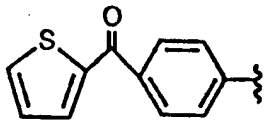
These and still other objects and associated advantages which will appear from the following description, are obtained with nitric esters having the following general formula:



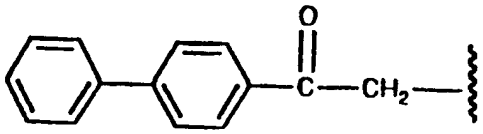
(I)

where:

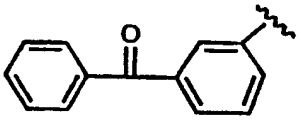
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among



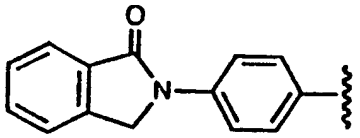
(II)



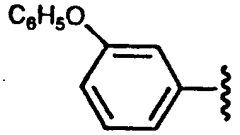
(III)



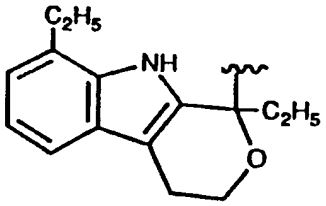
(IV)



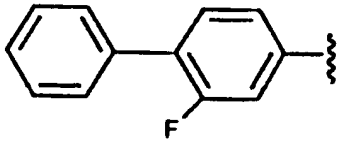
(VI)



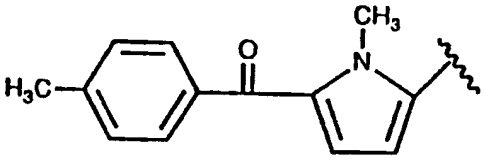
(VII)



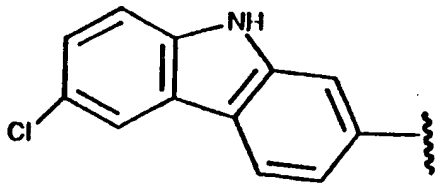
(VIII)



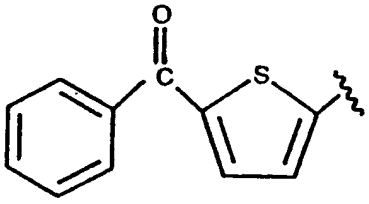
(IX)



(X)



(XXI)



(XXXV)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the general formula derivatives (I) allows to mantain the pharmacological activity characteristic of non steroid anti-inflammatory agents, while eliminating the adverse reactions caused by the treatment with such agents.

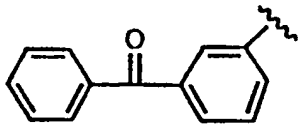
Besides, it has been observed that derivatives (I) are useful also in the treatment of various morbide conditions, such as, for instance, rheumatic diseases in general, disoders of immunologic nature, and can also assuage light-middle severity painful conditions of any kind.

More still, the derivatives (I) subject matter of this invention, are useful in the treatment of diseases of the cardio-vascular apparatus, and in particular in the treatment of miocardial and brain ischemiae as well as in artery thrombosis as anti-platelet aggregation agents.

Always according to this invention, a nitric ester of general formula (I) proved particularly advantageous, where:

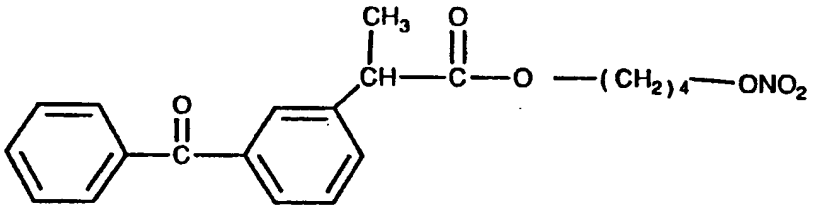
hydrogen is chosen as A and B, methyl is chosen as R_2,

and as R is chosen



(IV)

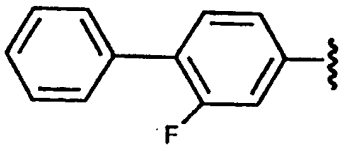
oxygen is chosen as y and n is equal to four, according to the following formula:



(XVIII)

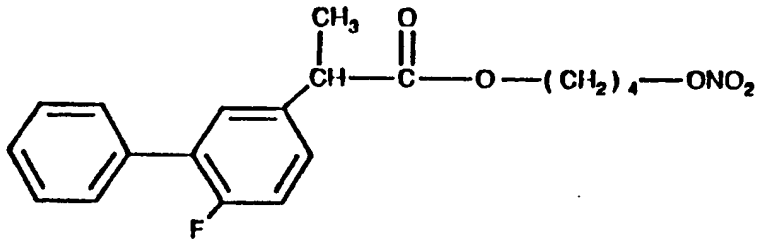
Also particularly advantageous according to this invention is the nitric ester of a general formula (I) where:

hydrogen is chosen as A and B, as R is chosen



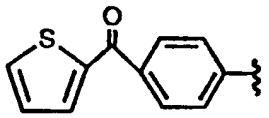
(IX)

methyl is chosen as R_2 oxygen is chosen as Y and n is equal to four, according to the following formula:

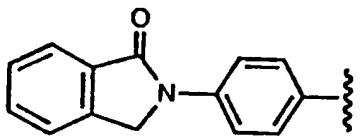


(XII)

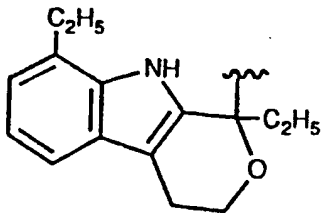
Still more, always according to the present invention, particularly advantageous are the nitric esters of general formula derivatives (I) where:
hydrogen is chosen as A and B, as R are chosen



(II)

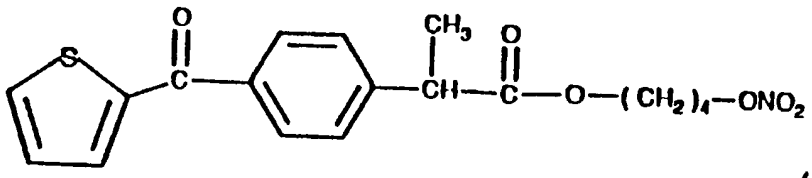


(VI)

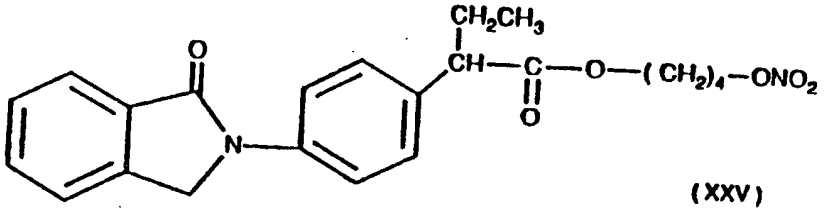


(VIII)

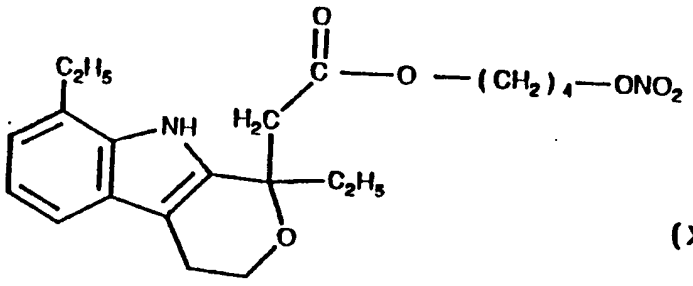
methyl, ethyl and hydrogen are chosen as R_2, oxygen is chosen as y and n is equal to four, according to the following formulae:



(XXIV)



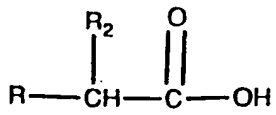
(XXV)



(XXVI)

For the preparation of general formula nitric esters (I), subject matter of the present invention, particularly advantageous proved to be a first process which, according to the invention, comprises the following steps:

- Preparation of the sodium salt of the products having the following general formula:

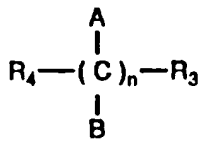


(XIV)

where R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV)

or preparation of derivatives (XIV) functionalized to the carboxyl group, such as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:



(XV)

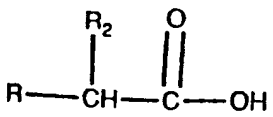
where:

R_4 is chosen among chlorine, bromine, NHR_6 with R_6 chosen among hydrogen, lineal or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_3 is chosen among chlorine, bromine, and iodine, and n is comprised between 1 and 10, obtaining in this way the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

Also a second process proved to be particularly advantageous which, always according to the present invention, comprises the following steps:

- Preparation of the sodium salt of derivatives having the following general formula:



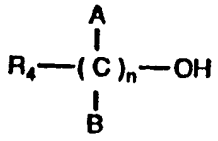
(XIV)

where R is chosen among:

(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or, alternatively, preparation of derivatives (XIV) functionalized to the carboxylic group, such as acidic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carbboxylic group, with a composition having the following general formula:



(XVI)

where:

R_4 is chosen among chlorine, bromine, NHR_6 with R_6 equal to hydrogen, or linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining in this way the relative monomeric esters or amides;

- Reaction of said monomeric esters or said amides with

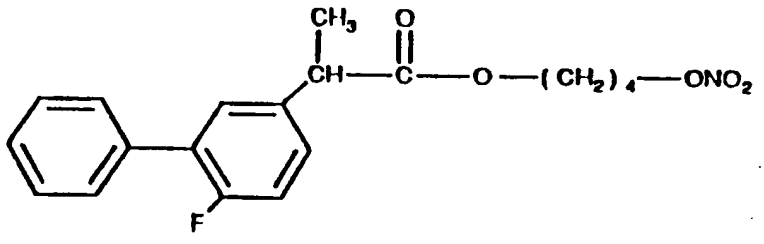
an halogenating composition such as PBr_3 or the like, obtaining in this way said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

The solvents utilized in the processes subject matter of this invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

The processes for the preparation of derivatives (I) subject matter of this invention, consist of a limited number of steps, allowing to obtain the products which derive from said processes in a short time and with satisfactory yields even on the industrial plane.

According to the processes subject matter of this invention, the preparation of a nitric ester having the following formula:



(XII)

proved to be particularly advantageous, which is prepared as described in the following example, given as a mere indication without limiting the protection scope of this invention.

EXAMPLE 1

a) 2 g of 2-fluoro-alpha-methyl-4-diphenylacetic acid were added to a solution constituted by 10 ml of methyl alcohol and 0.23 g of Na. The reaction mix was stirred for 5 minutes, then the solvent was evaporated under reduced pressure, obtaining the sodium salt of 2-fluoro-alpha-methyl-4-diphenylacetic acid.

b) The sodium salt of 2-fluoro-alpha-methyl-4-diphenilacetic acid obtained in this way was suspended in 20 ml of dimethylformamide and 3 ml of 1,4-dibromo-butane were added by dripping to this suspension. The reaction mix was stirred for 22 hours at room temperature, then the NaBr which had formed was filtered and the solvent was evaporated under reduced pressure. The residue so obtained was treated with methylene chloride and, after elimination by filtration of the insoluble residue, the methylene chloride was evaporated under reduced pressure, obtaining 3 g of a dry residue which was purified by silica gel chromatography, utilizing an eluent mix constituted by hexane/methylene chloride 1/1 (V/V).

The head fractions were collected, the solvent was evaporated under reduced pressure and 1.86 g of 2-fluoro-alpha-methyl-4-diphenylacetate of 4-bromobutyl

(XXII) were obtained.

IR (cm^{-1}): C=0,1470

^{1}-H-NMR (300 MHz) ($CDCl_3$) : 1.51ppm (d,3H); 1.56ppm (m,4H); 3,35ppm (t,2H); 3.61ppm (q,1H); 4.1ppm (t,2H); 7.05ppm (m,1H); 7.17ppm (s,1H); 7.3-7.55 (m, aromatics).

c) 1.2 g of $AgNO_3$ dissolved in 8.3 ml of acetonitrile were added to 1.86 g of (XXII), obtained as described under b) dissolved in 7.5 ml of acetonitrile. The reaction mix was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chroride. The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by diethylether/hexane 3/7 (V/V). The fractions containing the products were collected, the solvent was evaporated under reduced pressure and 1.2 g of nitric ester of 2-fluoro-alpha-methyl-4-diphenyl acetate of 4-hydroxybutyl (XII) were obtained.

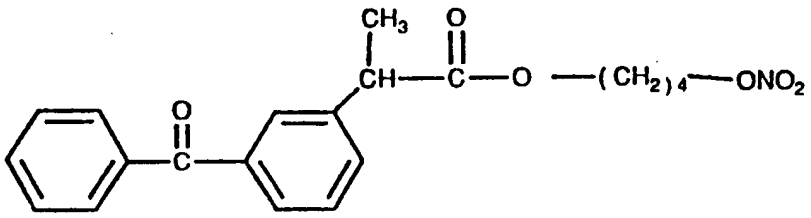
IR(cm^{-1}): C=0,1737; ONO_2, 1623, 1274.

^{1}H-NMR (300 MHz) ($CDCl_3$): 1.53ppm (d,3H); 1.72ppm (m,4H); 3.74ppm (q,1H); 4.13 ppm (t,2H); 4.4ppm (t,2H); 7.13ppm (t,2H, aromatics); 7.32-7.42ppm (m,4H, aromatics); 7.53ppm (m,2H, aromatics).

Mass spectrometry (i.e.): (M^+)361; (M+1-NO_2)316; 243;

199.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester having the following formula:



(XVIII)

proved particularly advantageous, which is prepared as described in the example shown hereunder, given as a mere indication without limiting the protection scope of this invention.

EXAMPLE 2

a) 10 g of 2-(3-benzoilphenyl)propionc acid were added to a solution constituted by 80 ml of methyl alcohol and 1.19 g of Na. The reaction mix was stirred for 15 minutes, then the solvent was evaporated under reduced pressure, obtaining a residue constituted by the sodium salt of 2-(3-benzoilphenyl)propionic acid.

b) 100 ml of dimethylformamide and 28.1 g of 1,4-dibromo-butane were added to the residue obtained in this way. The reaction mix was kept for 24 hours at room temperature and then the solvent was evaporated under reduced pressure. 40 ml of water and 60 ml of methylene

chloride were added to the residue obtained in this way and the organic phase was extracted and anhydrified on sodium sulphate and the solvent was evaporated under reduced pressure until a dry residue was obtained.

The residue was purified by silica gel chromatography, utilizing an eluent mix constituted by diethyl ether/hexane 1/1 (V/V). The head fractions were collected, the solvent was evaporated under reduced pressure and 8.8 g of 2-(3-benzoilphenyl)propionate of 4-bromobutyl (XXIII) were obtained.

^{1}H-NMR(200MHz) ($CDCl_3$): 1.53ppm (d,3H); 1.84ppm (m,4H); 3.32ppm (t,2H); 3.78ppm (q,1H); 4.09ppm (t,2H); 7.27 (m,1H, aromatics); 7.38-7.99 (m,8H aromatics).

Mass spectometry (i.e.): 388 (M^+); 309 (M^+-Br); 209.

c) 5.5 g of $AgNO_3$ dissolved in 38 ml of acetonitrile were added to 8.8 g of (XXIII) obtained as described under b) dissolved in 35 ml of acetonitrile. The reaction mix was stirred for 24 hours at room temperature and, having added 1.76 g of $AgNO_3$, the reaction mix was stirred for 24 more hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chloride.

The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by ethyl ether/hexane 3/7 (V/V).

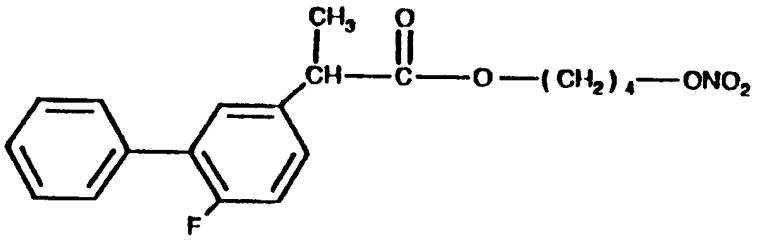
The fractions containing the product were collected, the solvent was evaporated under reduced pressure and 3.4 g of nitric ester of 2-(3-benzoilphenyl)propionate of 4-hydroxybutyl (XVIII) were obtained.

IR (cm^{-1}): C=0 1737; ONO_2, 1632, 1288; OCO, 1660.

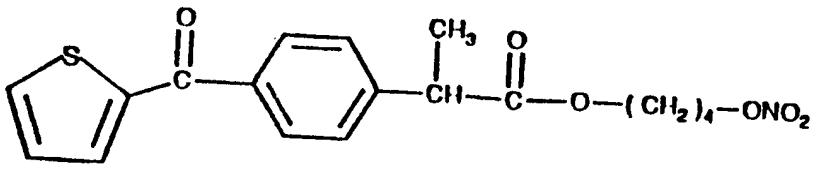
^1H-NMR (80 MHz) ($CDCl_3$): 1.48 ppm (d,3H); 1.64ppm (m,4H); 3.78ppm (q,1H); 4.08ppm (m,2H); 4.3ppm (m,2H); 7.3-7.81 (m, aromatics).

Mass spectrometry (i.e.): 371 (M^+); 309 (M^+-ONO_2); 255.

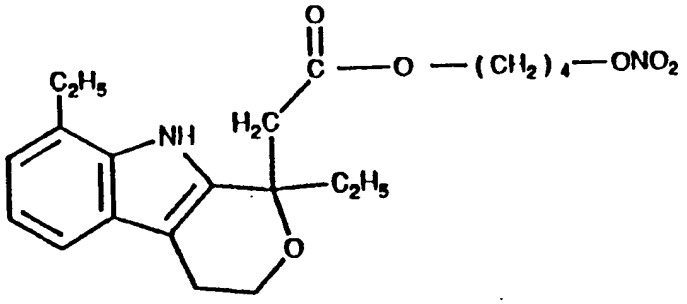
The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerogenicity, for instance of nitric esters having the following formulae, were tested by means of biological studies:



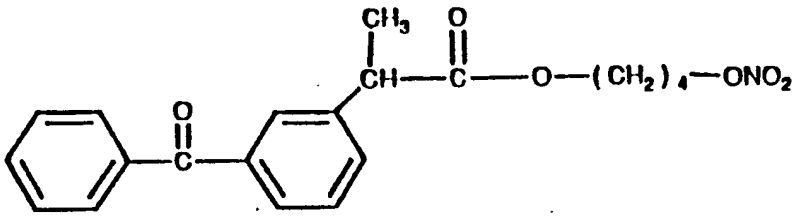
(XII)



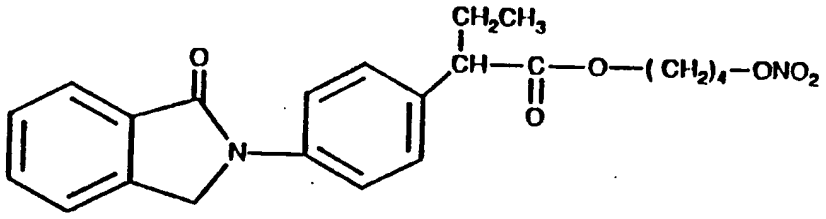
(XXIV)



(XXVI)



(XVIII)



(XXV)

The anti-inflammatory activity of said nitric esters was determined in Wistar rats utilizing the method of the carrageenan paw edema, as reported in C.A.WINTER, E.RISLEY, G.W.NUSS, Proc. Soc. Exp. Biol. Med. 111,544 (1962), while the anti-platelet aggregation activity of said derivatives was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al., Science 220,517 (1983).

The gastrointestainal ulcerability was evaluated by oral administration in the rat.

The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerability activity of said derivatives are given on Table 1, and are expressed, for each nitric ester indicated, as the power ratio relative to the corresponding acids non functionalized according to the general formula (I), according to this invention. Each value represents the mean of the values obtained by the treatment of 10 animals.

TABLE 1

COMPOUND STUDIED	ANTI-INFLAM. ACTIVITY	ANTI-AGGREG. ACTIVITY	GASTROINTESTINAL ULCERABILITY
(XVIII)	1,25	1,35	0,20
Ketoprofen	1	1	1
(XII)	1,25	1,15	0,35
Flurbiprofen	1	1	1
(XXIV)	1,20	1,30	0,35
Suprofen	1	1	1
(XXV)	1,05	1,25	0,30
Indobufen	1	1	1
(XXVI)	1,40	1,10	0,33
Etodolac	1	1	1

In particular, the derivatives (XVIII) and (XII) submitted to additional studies of a pharmacodynamical nature have given the following results, as shown in the following examples.

- RAT CARRAGEENAN PAW EDEMA. Both compounds (XVIII) and (XII) showed an efficacy comparable with the corresponding reference drugs Ketoprofen and Flurbiprofen, the effective doses being in the 1 to 10 mg/kg p.o. range.
- RAT ADJUVANT ARTHRITIS. Animals treated for 19 consecutive days (days 3 through 21 after adjuvant injection) with 3 mg/kg p.o. of either compound (XVIII) or (XII) and their corresponding reference compound showed a significant and comparative reduction in the arthritic symptomatology compared to controls.
- MOUSE PHENYLQUINONE WRITHING. At doses ranging from 3 to 10 mg/kg p.o., compound (XVIII) and (XII) proved fully effective and their efficaciousness was almost comparable with that of the corresponding reference compounds.
- IN VIVO PLATELET AGGREGATION. While both compositions - (XVIII) and Flurbiprofen, when administered at the dose of 20 mg/kg p. o. in the rat, inhibited collagen-induced platelet aggregation, the former (66% inhibition versus controls) was significantly more effective than the latter (40%).

BIOCHEMISTRY

- PROSTAGLANDIN SYNTHESIS IN THE INFLAMMATORY EXUDATE.

Subcutaneous implantation of carrageenan sponge elicits the infiltration of inflammatory cells, as reported in Nature 284, 271 (1980). Both compounds , (XVIII) and (XII) when administered at the dose of 20 mg/kg p.o. inhibited the formation of prostaglandin E2 in exudate by more than 75% compared with controls and have shown comparative efficacy to the corresponding reference compounds Ketoprofen and Flurbiprofen.

- GASTRIC PROSTAGLANDIN SYNTHESIS. Both compounds, (XVIII) and (XII) were studied for prostaglandin synthesis at the same doses (5-20 mg/kg p.o.) utilized for gastric injuries studies. They inhibited significantly and comparatively to the corresponding reference compounds Ketoprofen and Flurbiprofen, the synthesis of prostaglandin E2, the percent of inhibition being more than 90% at the highest dose.

- NO RELEASE. Evidence that compounds (XVIII) and (XII) released nitric oxide after their administration was obtained by measurements of plasma nitrate/nitrite levels, as reported in J. Clin. Invest., 85, 264 (1990). One hour after the administration of either (XVIII) or (XII) compound, the plasma nitrate/nitrite levels had significantly increased by more than 50%. Ketoprofen or Flurbiprofen did not affect plasma nitrate/nitrite levels significantly.

Besides, additional biological studies were performed on derivatives (XII) and (XVIII); said studies have

provided the following results.

GASTROINTESTINAL TOLERABILITY

- RAT GASTRIC MUCOSA INJURY. (XVIII) and (XII) were studied in comparison with the corresponding reference compounds Ketoprofen and Flurbiprofen at doses ranging from 3 to 30 mg/kg p.o., both (XII) and (XVIII) compounds being significantly better tolerated than reference compounds. Ketoprofen or Flurbiprofen caused the onset of gastric damages already at the dose of 3 mg/kg, the severity of such damages being dose-dependent, while (XVIII) or (XII) compounds were well tolerated even at the dose of 30 mg/kg.

The histological evaluation confirmed these findings. Similar differences in the capacity of these compounds to cause gastric and small intestine injury were also observed upon repeated administration of the compounds.

- GASTRIC LEUKOCYTE ADHERENCE/VESSEL DIAMETER. An early event in the pathogenesis of NSAID-induced gastric mucosa injury is the adherence of leukocytes to the endothelium of post-capillary venules, as reported in Gastroenterology 103, 146 (1992); Trends Pharmacol. Sci. 13, 129 (1992); Am.J. Physiol. 262, G903 (1992). Using intravital microscopy, the leucokocyte adherence to mesenteric post-capillary venules could be quantified prior to and during a one hour period after the administration of NSAID. Unlike Ketoprofen or Flurbiprofen, (XVIII) or (XII) did not induce significant

leukocyte adherence, while increasing the diameter of vessels significantly. No changes in blood pressure were observed.

GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (XVIII) or (XII) was performed in comparison with Ketroprofen or Flurbiprofen. No relevant additional adverse reactions were observed affecting the central nervous, autonomic, cardiovascular, respiratory and gastrointestinal systems.

TOXICOLOGY

- ACUTE TOXICOLOGY IN RODENTS.

The acute toxicity of said derivatives (XVIII), (XXIV), (XXV), (XII) and (XXVI) was then evaluated by p.o. administration of a single dose of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), utilizing, for each derivative, groups of 10 Swiss mice. Death incidence and the onset of toxic symptoms were reported for a period of 14 days.

Even after administration of a dose of 100 mg/kg of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), no apparent toxicity symptoms were noticed in the animals studied.

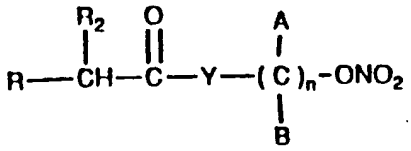
In particular, preliminary studies on compounds (XVIII) or (XII) were performed in the mouse by two administration routes. No evident toxicity was observed in the animals treated with oral or intraperitoneal doses of

300 mg/kg of either compound.

- MAXIMUM TOLERATED DOSE IN NON RODENTS. Preliminary studies indicate that compounds (XVIII) and (XII) were very well tolerated in this animal species that is known to be particularly sensitive to this class of compounds. The animals were administered increasing oral doses up to 30 mg/kg of either compound and no apparent symptoms were observed, while the reference compounds Ketoprofen and Flurbiprofen, administred at the dose of 10 mg/kg caused the death of the animals.

CLAIMS

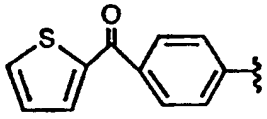
1. Nitric esters characterized in that they have the following general formula:



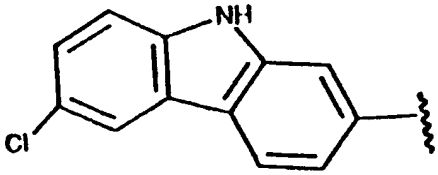
(I)

where:

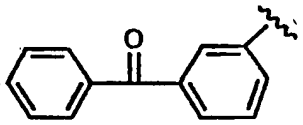
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



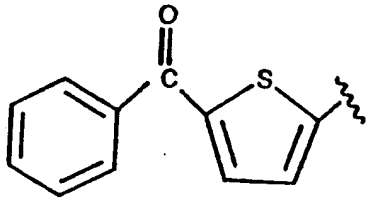
(II)



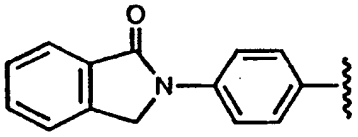
(XXI)



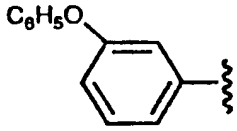
(IV)



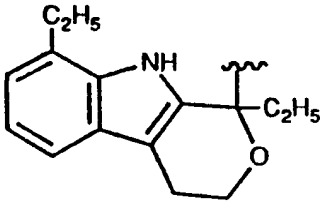
(XXXV)



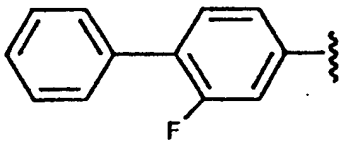
(VI)



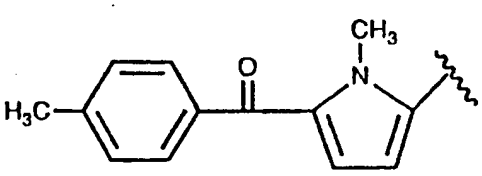
(VII)



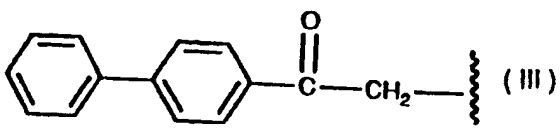
(VIII)



(IX)



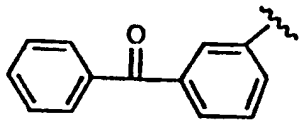
(X)



(III)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

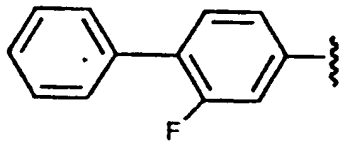
2. Nitric ester according to claim 1, characterized in that R is:



(IV)

R_2 is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

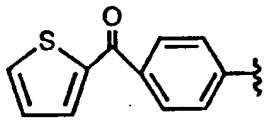
3. Nitric ester according to claim 1, characterized in that R is equal to:



(IX)

R_2 is equal to methyl, Y is equal to oxygen, A and B are equal to hydrogen and n is equal to four.

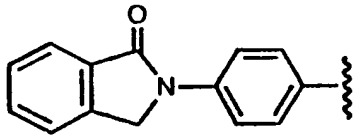
4. Nitric ester according to claim 1, characterized in that R is equal to:



(II)

R_2 is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

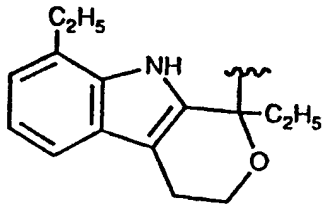
5. Nitric ester according to claim 1, characterized in that R is equal to:



(VI)

R_2 is equal to ethyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

6. Nitric ester according to claim 1, characterized in that R is equal to:



(VIII)

R_2 is equal to hydrogen, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

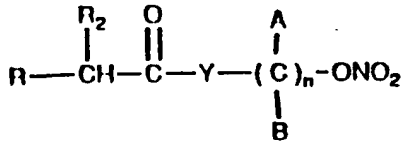
7. Nitric esters according to claim 1, characterized in that they are utilizable in pharmaceutics as anti-

inflammatory agents.

8. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic diseases, disorders of immunologic nature, and slight-middle severity painful conditions.

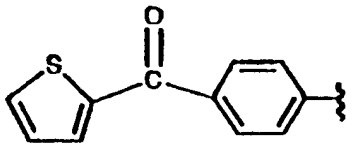
9. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of diseases affecting the cardiovascular system, the treatment of miocardial and brain ischemiae and in cases of arterial thromobosis as platelet anti-aggregation agents.

10. Process for the preparation of nitric esters according to claim 1 and having the following general formula:

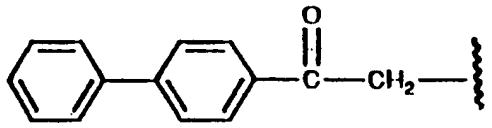


(I)

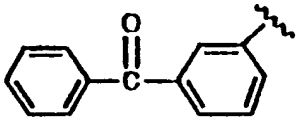
where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



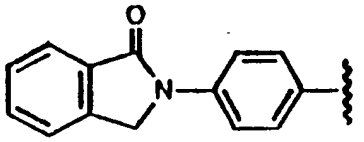
(II)



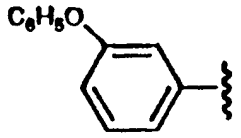
(III)



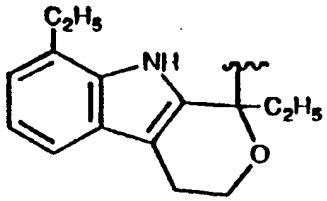
(IV)



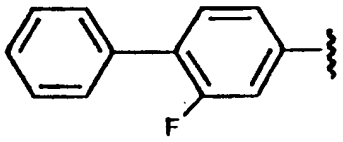
(VI)



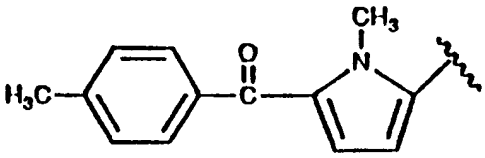
(VII)



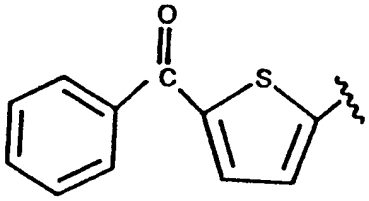
(VIII)



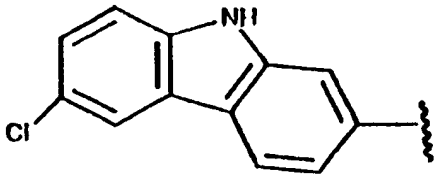
(IX)



(X)



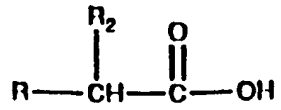
(XXXV)



(XXI)

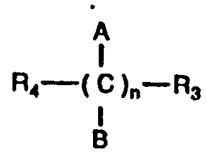
R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl chain, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



(XIV)

where R is chosen among the following structures:
(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV),
or preparation of derivatives (XIV) functionalized to the carboxylic group as acilic chlorides, anhydrides or the like;
- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:



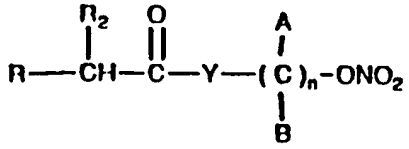
(XV)

where:
R_4 is chosen among chlorine, bromine, NHR_6, with R_6 hydrogen linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted

or non substituted alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

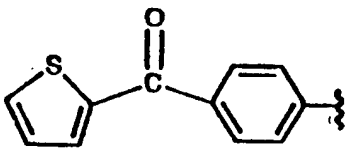
11. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



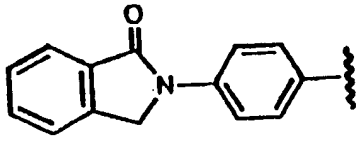
(I)

where:

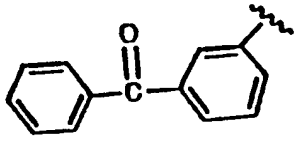
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among:



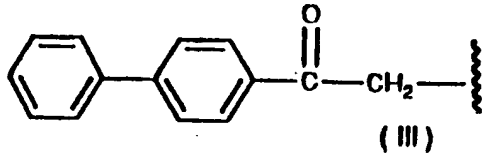
(II)



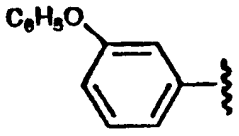
(VI)



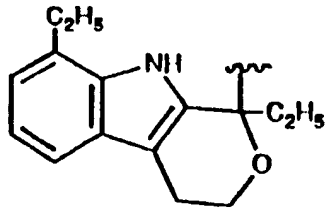
(IV)



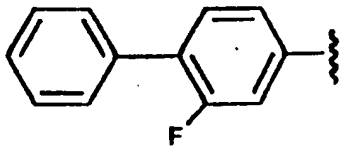
(III)



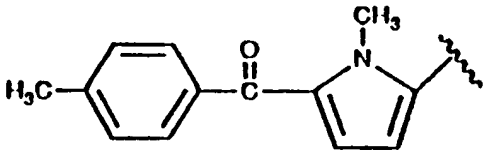
(VII)



(VIII)

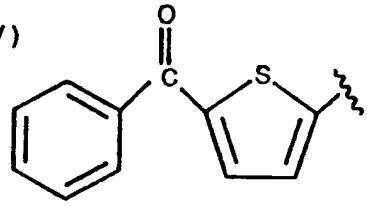


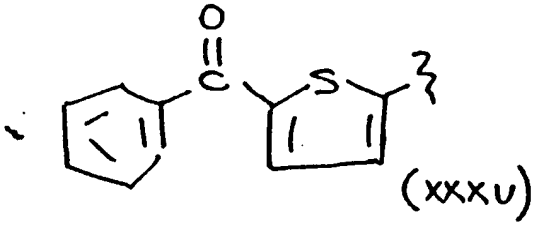
(IX)



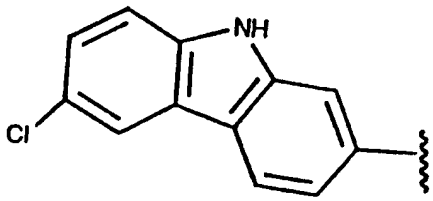
(X)

(XXXV)





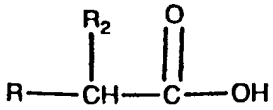
(XXXV)



(XXI)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:



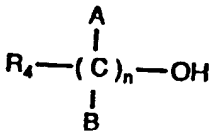
(XIV)

where R is chosen among the following structures:

(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV),

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or preparation of derivatives (XIV) functionalized to the caboxylic group, such as acilic chlorides, anhydrides and the like;

- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:



(XVI)

where:

R_4 is chosen among chlorine, bromine, NHR_6, with R_6 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr_3 or the like, obtaining said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 93/03193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C203/04 A61K31/21 C07D333/22 C07D209/46 C07D491/04
A61K31/40 A61K31/38 C07D207/337 C07D209/88 C07D333/24
A61K31/16 C07C235/78 C07C235/34 C07C233/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 359 335 (CEDONA PHARMACEUTICALS B.V.) 21 March 1990 see page 4; claims	1,9
A	WO,A,92 01668 (ITALFARMACO S.P.A.) 6 February 1992 see claims	1,9
A	EP,A,0 300 400 (FUJISAWA PHARMACEUTICAL CO., LTD.) 25 January 1989 see claims	1,9
A	US,A,4 585 877 (C.A. DEMERSON ET AL.) 29 April 1986 see example 4	1,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1994	16. 02. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bonnevalle, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 93/03193

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 988 728 (S.H.GERSON ET AL.) 29 January 1991 see the whole document	1,7
A	FR,A,2 612 185 (FARMITALIA CARLO ERBA S.R.L.) 16 September 1988 see page 12; claims	1,7,9

1

INTERNATIONAL SEARCH REPORT

nformation on patent family members

Inter nal Application No
PCT/EP 93/03193

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0359335	21-03-90	NL-A-	8802276	02-04-90
		AU-B-	638413	01-07-93
		AU-A-	4133089	22-03-90
		JP-A-	2134316	23-05-90
		US-A-	5049694	17-09-91
WO-A-9201668	06-02-92	AU-A-	8097491	18-02-92
		EP-A-	0540544	12-05-93
EP-A-0300400	25-01-89	AU-B-	623858	28-05-92
		AU-A-	1919988	27-01-89
		JP-C-	1666528	29-05-92
		JP-A-	2028167	30-01-90
		JP-B-	3031709	08-05-91
		SU-A-	1706388	15-01-92
		SU-A-	1760984	07-09-92
		US-A-	4923886	08-05-90
		US-A-	5010093	23-04-91
US-A-4585877	29-04-86	NONE		
US-A-4988728	29-01-91	NONE		
FR-A-2612185	16-09-88	AT-B-	392068	25-01-91
		AU-B-	605253	10-01-91
		AU-A-	1267988	08-09-88
		BE-A-	1003280	18-02-92
		CH-A-	675419	28-09-90
		DE-A-	3807595	22-09-88
		GB-A,B	2204579	16-11-88
		JP-A-	63238058	04-10-88
		NL-A-	8800575	03-10-88
		SE-A-	8800846	11-09-88

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07C 203/04, A61K 31/21, C07D 333/22, 209/46, 491/04, A61K 31/40, 31/38, C07D 207/337, 209/88, 333/24, A61K 31/16, C07C 235/78, 235/34, 233/21

A1

(11) International Publication Number: WO 94/12463

(43) International Publication Date: 9 June 1994 (09.06.94)

(21) International Application Number: PCT/EP93/03193

(22) International Filing Date: 15 November 1993 (15.11.93)

(30) Priority Data:
MI92A002699 26 November 1992 (26.11.92) IT

(71) Applicant *(for all designated States except US)*: HCT-HEALTH CARE TRADING LTD. [IE/IE]; Dame Street, Dublin 2 (IE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ARENA, Barbara [IT/IT]; Via Toti, 22, I-20052 Monza (IT).

(74) Agent: TRUPIANO, Roberto; Brevetti Europa S.r.l., Piazza Bernini, 6, I-20133 Milano (IT).

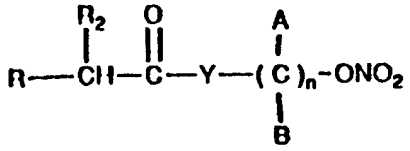
(81) Designated States: AU, BR, CA, CZ, FI, HU, JP, KP, KR, NO, NZ, PL, RO, RU, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

(57) Abstract

Nitric esters with pharmacological activity having general formula (I), their pharmaceutical utilisation and process for their preparation.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

NITRIC ESTERS HAVING A PHARMACOLOGICAL ACTIVITY AND PROCESS FOR THEIR PREPARATION

Object of the present invention are nitric esters with an anti-inflammatory and/or anti-platelet aggregation activity, their pharmaceutical utilization and the process for their preparation.

PRIOR ART

Some derivatives of propionic acid, such as for instance 2-(-3-benzoylphenyl)propionic acid, commonly known as ketoprofen, have been used for a long time as pharmaceutical preparations for their anti-inflammatory activity and are sold on the different international markets since many years. The process for the preparation of 2-(3-benzoylphenyl)propionic acid has been described in the South African patent n° 68 00,524, corresponding to the US patent 3,641,127; in the French patent n° M6444 and also in C.A. 75,5528m (1971); G.A. PINNA et al., FARMACO Ed. Sci. 35,684 (1980); while the pharmacokinetics in humans is described in T. ISHIZAKI et al., Eur.J.Clin. Pharmacol. 18,407 (1980). The use of derivatives of propionic acid, such as, for instance, keptofren, as well as the use of other products which are utilized as anti-inflammatory agents, involves, as known, severe adverse reactions, for instance in the gastrointestinal apparatus, as well as possible damages to the liver and the kidneys.

There is much experimental evidence [S. MONCADA, R.M.J.PALMER, E.A.HIGGS, Pharmacological Reviews,

43(2), 109 (1991); T.H.LUSHER, C.M.BOULANGER, Y.DOHI, Z.YANG, Hypertension, 19,117 (1992)], on whose basis the integrity of vasal endothelium is thought to be a basic barrier against the onset of pathological processes in several organs and apparatuses.

Such protection barrier, and therefore the integrity of the vasal endothelium, is ensured physiologically by the presence of nitric oxide and prostacyclin.

The treatment with non steroid drugs having an anti-inflammatory activity, such as, for instance, 2-(3-benzoylphenyl)propionic acid or ketoprofen, causes the inhibition of cyclo-oxygenase, an enzyme which syntesizes the precursor of prostacyclin.

As a consequence, having so inhibited the production of prostacyclin, the reserve of same in the tissues is markedly depauperated, and therefore the integrity of vasal endothelium is compromised.

As said, because of this endothelial damage due to the reduction of prostacyclin, diffuse pathological process break out which affect the gastrointestinal apparatus, liver and kidneys.

OBJECTS OF THE INVENTION

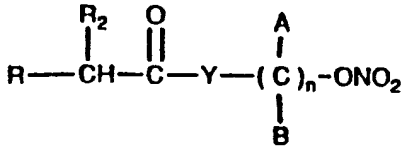
Object of the present invention is that to provide a group of products which, while ensuring the maintenance of the pharmacological activity characteristic of the known anti-inflammatory agents, are capable of eliminating the adverse reactions caused by the treatment with

said agents.

Another object of the present invention is the realization of a process for the preparation of a group of products having an anti-inflammatory activity while being exempt from the adverse reations which are typical of anti-inflammatory agents.

DESCRIPTION OF THE INVENTION

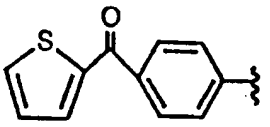
These and still other objects and associated advantages which will appear from the following description, are obtained with nitric esters having the following general formula:



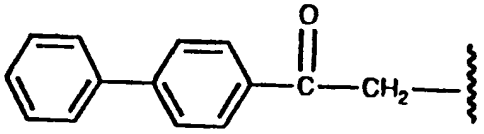
(I)

where:

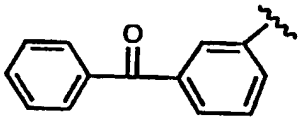
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among



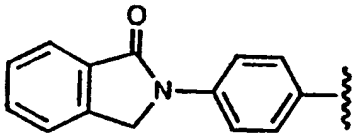
(II)



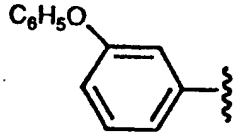
(III)



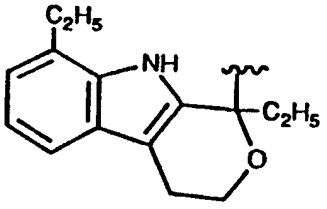
(IV)



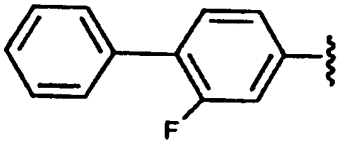
(VI)



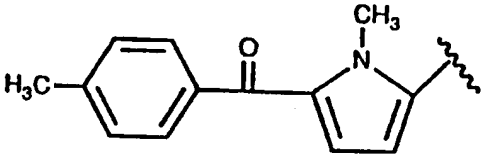
(VII)



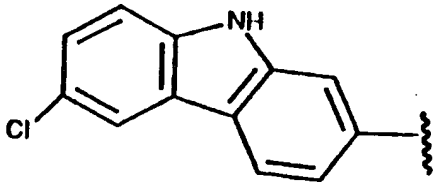
(VIII)



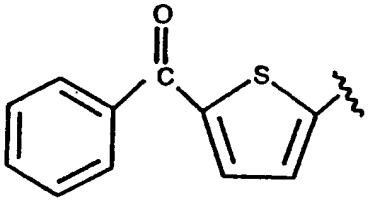
(IX)



(X)



(XXI)



(XXXV)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group and n is comprised between 1 and 10.

In fact, it has been observed that the introduction of a group such as a terminal nitric ester in the general formula derivatives (I) allows to mantain the pharmacological activity characteristic of non steroid anti-inflammatory agents, while eliminating the adverse reactions caused by the treatment with such agents.

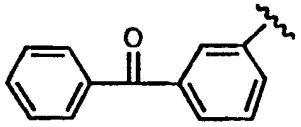
Besides, it has been observed that derivatives (I) are useful also in the treatment of various morbide conditions, such as, for instance, rheumatic diseases in general, disoders of immunologic nature, and can also assuage light-middle severity painful conditions of any kind.

More still, the derivatives (I) subject matter of this invention, are useful in the treatment of diseases of the cardio-vascular apparatus, and in particular in the treatment of miocardial and brain ischemiae as well as in artery thrombosis as anti-platelet aggregation agents.

Always according to this invention, a nitric ester of general formula (I) proved particularly advantageous, where:

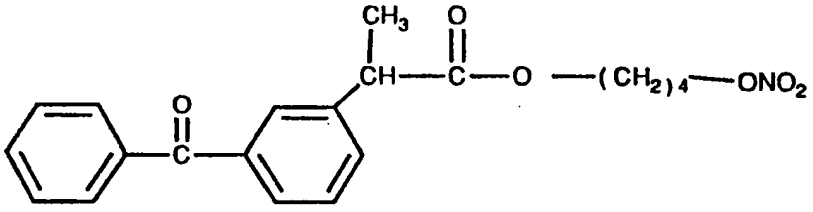
hydrogen is chosen as A and B, methyl is chosen as R_2,

and as R is chosen



(IV)

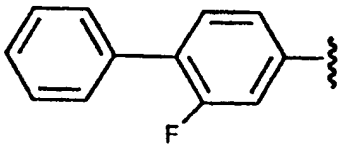
oxygen is chosen as y and n is equal to four, according to the following formula:



(XVIII)

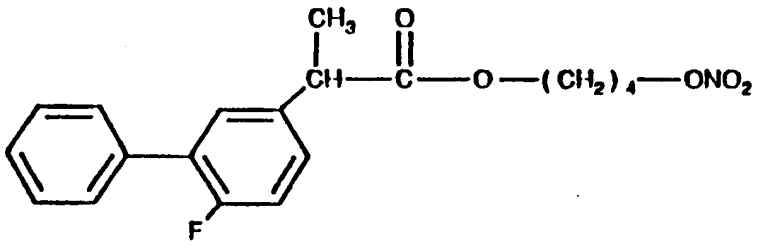
Also particularly advantageous according to this invention is the nitric ester of a general formula (I) where:

hydrogen is chosen as A and B, as R is chosen



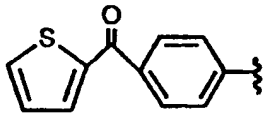
(IX)

methyl is chosen as R_2 oxygen is chosen as Y and n is equal to four, according to the following formula:

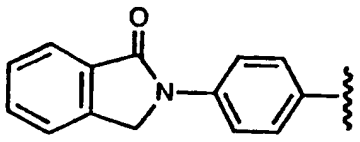


(XII)

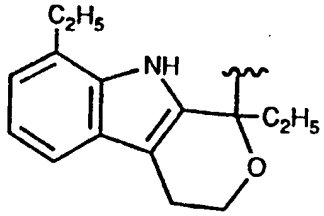
Still more, always according to the present invention, particularly advantageous are the nitric esters of general formula derivatives (I) where:
hydrogen is chosen as A and B, as R are chosen



(II)

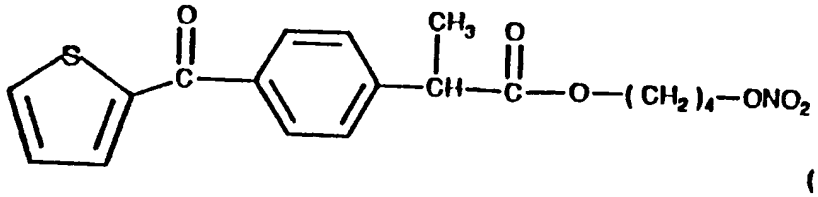


(VI)

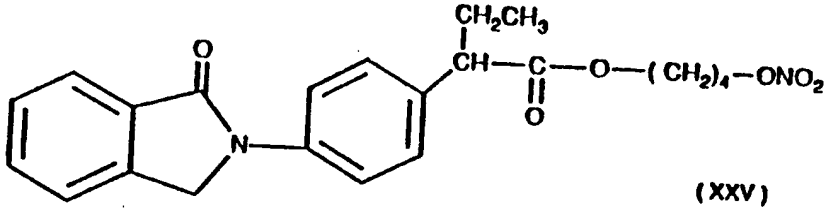


(VIII)

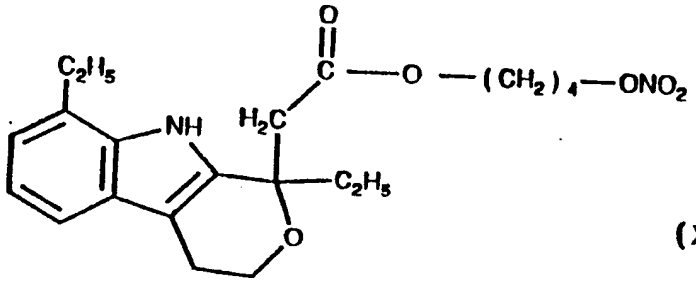
methyl, ethyl and hydrogen are chosen as R_2, oxygen is chosen as y and n is equal to four, according to the following formulae:



(XXIV)



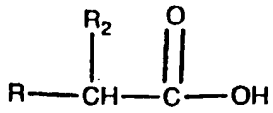
(XXV)



(XXVI)

For the preparation of general formula nitric esters (I), subject matter of the present invention, particularly advantageous proved to be a first process which, according to the invention, comprises the following steps:

- Preparation of the sodium salt of the products having the following general formula:

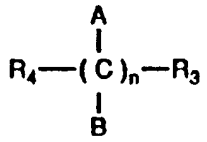


(XIV)

where R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV)

or preparation of derivatives (XIV) functionalized to the carboxyl group, such as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carboxylic group, with a composition having the following general formula:



(XV)

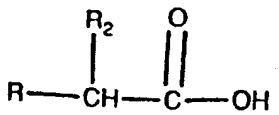
where:

R_4 is chosen among chlorine, bromine, NHR_6 with R_6 chosen among hydrogen, lineal or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_3 is chosen among chlorine, bromine, and iodine, and n is comprised between 1 and 10, obtaining in this way the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

Also a second process proved to be particularly advantageous which, always according to the present invention, comprises the following steps:

- Preparation of the sodium salt of derivatives having the following general formula:



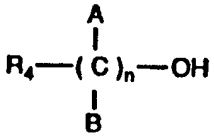
(XIV)

where R is chosen among:

(II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or, alternatively, preparation of derivatives (XIV) functionalized to the carboxylic group, such as acidic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or between said derivatives (XIV) functionalized to the carbboxylic group, with a composition having the following general formula:



(XVI)

where:

R_4 is chosen among chlorine, bromine, NHR_6 with R_6 equal to hydrogen, or linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining in this way the relative monomeric esters or amides;

- Reaction of said monomeric esters or said amides with

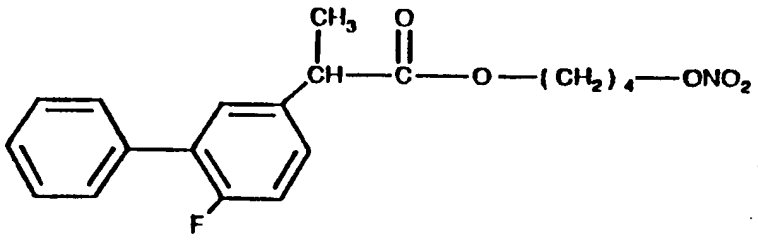
an halogenating composition such as PBr_3 or the like, obtaining in this way said monomeric esters or said amides characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group, with a nitrating agent such as $AgNO_3$ or the like, obtaining in this way nitric esters of derivatives (I).

The solvents utilized in the processes subject matter of this invention are preferably chosen among chloroform, methylene chloride, acetonitrile, dimethylformamide, tetrahydrofuran, 1,4-dioxane and the like.

The processes for the preparation of derivatives (I) subject matter of this invention, consist of a limited number of steps, allowing to obtain the products which derive from said processes in a short time and with satisfactory yields even on the industrial plane.

According to the processes subject matter of this invention, the preparation of a nitric ester having the following formula:



(XII)

proved to be particularly advantageous, which is prepared as described in the following example, given as a mere indication without limiting the protection scope of this invention.

EXAMPLE 1

a) 2 g of 2-fluoro-alpha-methyl-4-diphenylacetic acid were added to a solution constituted by 10 ml of methyl alcohol and 0.23 g of Na. The reaction mix was stirred for 5 minutes, then the solvent was evaporated under reduced pressure, obtaining the sodium salt of 2-fluoro-alpha-methyl-4-diphenylacetic acid.

b) The sodium salt of 2-fluoro-alpha-methyl-4-diphenilacetic acid obtained in this way was suspended in 20 ml of dimethylformamide and 3 ml of 1,4-dibromo-butane were added by dripping to this suspension. The reaction mix was stirred for 22 hours at room temperature, then the NaBr which had formed was filtered and the solvent was evaporated under reduced pressure. The residue so obtained was treated with methylene chloride and, after elimination by filtration of the insoluble residue, the methylene chloride was evaporated under reduced pressure, obtaining 3 g of a dry residue which was purified by silica gel chromatography, utilizing an eluent mix constituted by hexane/methylene chloride 1/1 (V/V).

The head fractions were collected, the solvent was evaporated under reduced pressure and 1.86 g of 2-fluoro-alpha-methyl-4-diphenylacetate of 4-bromobutyl

(XXII) were obtained.

IR (cm^{-1}): C=0,1470

^{1}-H-NMR (300 MHz) ($CDCl_3$) : 1.51ppm (d,3H); 1.56ppm (m,4H); 3,35ppm (t,2H); 3.61ppm (q,1H); 4.1ppm (t,2H); 7.05ppm (m,1H); 7.17ppm (s,1H); 7.3-7.55 (m, aromatics).

c) 1.2 g of $AgNO_3$ dissolved in 8.3 ml of acetonitrile were added to 1.86 g of (XXII), obtained as described under b) dissolved in 7.5 ml of acetonitrile. The reaction mix was stirred for 48 hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chroride. The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by diethylether/hexane 3/7 (V/V). The fractions containing the products were collected, the solvent was evaporated under reduced pressure and 1.2 g of nitric ester of 2-fluoro-alpha-methyl-4-diphenyl acetate of 4-hydroxybutyl (XII) were obtained.

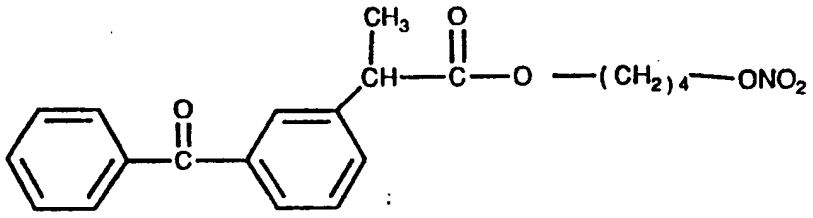
IR(cm^{-1}): C=0,1737; ONO_2, 1623, 1274.

^{1}H-NMR (300 MHz) ($CDCl_3$): 1.53ppm (d,3H); 1.72ppm (m,4H); 3.74ppm (q,1H); 4.13 ppm (t,2H); 4.4ppm (t,2H); 7.13ppm (t,2H, aromatics); 7.32-7.42ppm (m,4H, aromatics); 7.53ppm (m,2H, aromatics).

Mass spectrometry (i.e.): (M^+)361; (M+1-NO_2)316; 243;

199.

Always according to the processes subject matter of the present invention, also the preparation of a nitric ester having the following formula:



(XVIII)

proved particularly advantageous, which is prepared as described in the example shown hereunder, given as a mere indication without limiting the protection scope of this invention.

EXAMPLE 2

a) 10 g of 2-(3-benzoilphenyl)propionc acid were added to a solution constituted by 80 ml of methyl alcohol and 1.19 g of Na. The reaction mix was stirred for 15 minutes, then the solvent was evaporated under reduced pressure, obtaining a residue constituted by the sodium salt of 2-(3-benzoilphenyl)propionic acid.

b) 100 ml of dimethylformamide and 28.1 g of 1,4-dibromo-butane were added to the residue obtained in this way. The reaction mix was kept for 24 hours at room temperature and then the solvent was evaporated under reduced pressure. 40 ml of water and 60 ml of methylene

chloride were added to the residue obtained in this way and the organic phase was extracted and anhydrified on sodium sulphate and the solvent was evaporated under reduced pressure until a dry residue was obtained.

The residue was purified by silica gel chromatography, utilizing an eluent mix constituted by diethyl ether/hexane 1/1 (V/V). The head fractions were collected, the solvent was evaporated under reduced pressure and 8.8 g of 2-(3-benzoilphenyl)propionate of 4-bromobutyl (XXIII) were obtained.

^{1}H-NMR(200MHz) ($CDCl_3$): 1.53ppm (d,3H); 1.84ppm (m,4H); 3.32ppm (t,2H); 3.78ppm (q,1H); 4.09ppm (t,2H); 7.27 (m,1H, aromatics); 7.38-7.99 (m,8H aromatics).

Mass spectometry (i.e.): 388 (M^+); 309 (M^+-Br); 209.

c) 5.5 g of $AgNO_3$ dissolved in 38 ml of acetonitrile were added to 8.8 g of (XXIII) obtained as described under b) dissolved in 35 ml of acetonitrile. The reaction mix was stirred for 24 hours at room temperature and, having added 1.76 g of $AgNO_3$, the reaction mix was stirred for 24 more hours at room temperature and then filtered. The solvent was evaporated from the resulting solution under reduced pressure, obtaining a residue which was treated with methylene chloride.

The mix obtained in this way was filtered again and the organic phase was purified by silica gel pressure chromatography, utilizing an eluent mix constituted by ethyl ether/hexane 3/7 (V/V).

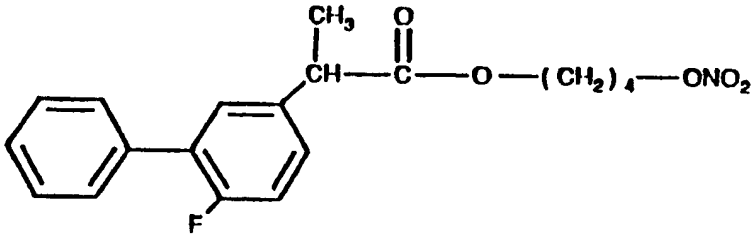
The fractions containing the product were collected, the solvent was evaporated under reduced pressure and 3.4 g of nitric ester of 2-(3-benzoilphenyl)propionate of 4-hydroxybutyl (XVIII) were obtained.

IR (cm^{-1}): C=0 1737; ONO_2, 1632, 1288; OCO, 1660.

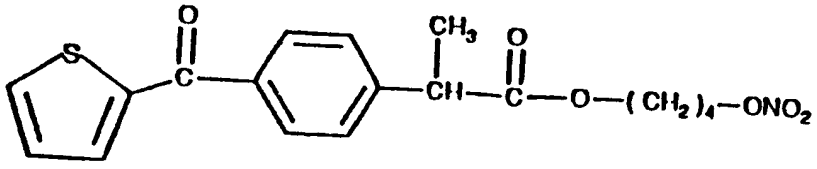
^1H-NMR (80 MHz) ($CDCl_3$): 1.48 ppm (d,3H); 1.64ppm (m,4H); 3.78ppm (q,1H); 4.08ppm (m,2H); 4.3ppm (m,2H); 7.3-7.81 (m, aromatics).

Mass spectrometry (i.e.): 371 (M^+); 309 (M^+-ONO_2); 255.

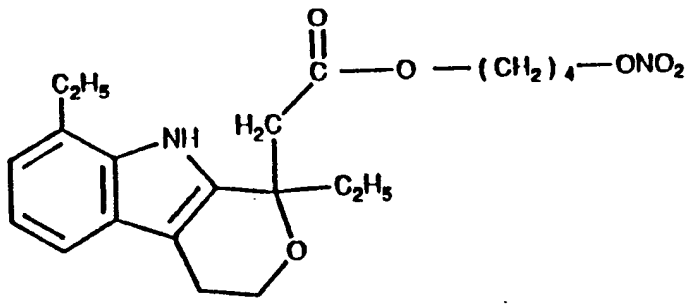
The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerogenicity, for instance of nitric esters having the following formulae, were tested by means of biological studies:



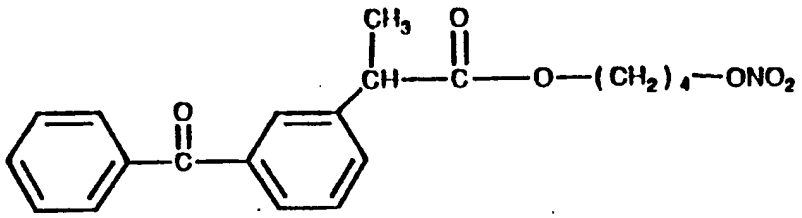
(XII)



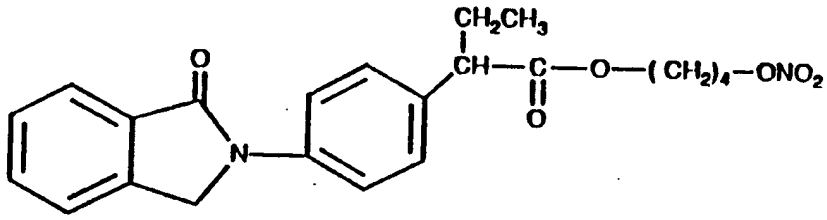
(XXIV)



(XXVI)



(XVIII)



(XXV)

The anti-inflammatory activity of said nitric esters was determined in Wistar rats utilizing the method of the carrageenan paw edema, as reported in C.A.WINTER, E.RISLEY, G.W.NUSS, Proc. Soc. Exp. Biol. Med. 111,544 (1962), while the anti-platelet aggregation activity of said derivatives was determined on human platelets stimulated by arachidonic acid, according to the method described by V.BERTELE et al., Science 220,517 (1983).

The gastrointestainal ulcerability was evaluated by oral administration in the rat.

The anti-inflammatory and anti-platelet aggregation activity as well as the gastrointestinal ulcerability activity of said derivatives are given on Table 1, and are expressed, for each nitric ester indicated, as the power ratio relative to the corresponding acids non functionalized according to the general formula (I), according to this invention. Each value represents the mean of the values obtained by the treatment of 10 animals.

TABLE 1

COMPOUND STUDIED	ANTI-INFLAM. ACTIVITY	ANTI-AGGREG. ACTIVITY	GASTROINTESTINAL ULCERABILITY
(XVIII)	1,25	1,35	0,20
Ketoprofen	1	1	1
(XII)	1,25	1,15	0,35
Flurbiprofen	1	1	1
(XXIV)	1,20	1,30	0,35
Suprofen	1	1	1
(XXV)	1,05	1,25	0,30
Indobufen	1	1	1
(XXVI)	1,40	1,10	0,33
Etodolac	1	1	1

In particular, the derivatives (XVIII) and (XII) submitted to additional studies of a pharmacodynamical nature have given the following results, as shown in the following examples.

- RAT CARRAGEENAN PAW EDEMA. Both compounds (XVIII) and (XII) showed an efficacy comparable with the corresponding reference drugs Ketoprofen and Flurbiprofen, the effective doses being in the 1 to 10 mg/kg p.o. range.
- RAT ADJUVANT ARTHRITIS. Animals treated for 19 consecutive days (days 3 through 21 after adjuvant injection) with 3 mg/kg p.o. of either compound (XVIII) or (XII) and their corresponding reference compound showed a significant and comparative reduction in the arthritic symptomatology compared to controls.
- MOUSE PHENYLQUINONE WRITHING. At doses ranging from 3 to 10 mg/kg p.o., compound (XVIII) and (XII) proved fully effective and their efficaciousness was almost comparable with that of the corresponding reference compounds.
- IN VIVO PLATELET AGGREGATION. While both compositions - (XVIII) and Flurbiprofen, when administered at the dose of 20 mg/kg p. o. in the rat, inhibited collagen-induced platelet aggregation, the former (66% inhibition versus controls) was significantly more effective than the latter (40%).

BIOCHEMISTRY

- PROSTAGLANDIN SYNTHESIS IN THE INFLAMMATORY EXUDATE.

Subcutaneous implantation of carrageenan sponge elicits the infiltration of inflammatory cells, as reported in Nature 284, 271 (1980). Both compounds , (XVIII) and (XII) when administered at the dose of 20 mg/kg p.o. inhibited the formation of prostaglandin E2 in exudate by more than 75% compared with controls and have shown comparative efficacy to the corresponding reference compounds Ketoprofen and Flurbiprofen.

- GASTRIC PROSTAGLANDIN SYNTHESIS. Both compounds, (XVIII) and (XII) were studied for prostaglandin synthesis at the same doses (5-20 mg/kg p.o.) utilized for gastric injuries studies. They inhibited significantly and comparatively to the corresponding reference compounds Ketoprofen and Flurbiprofen, the synthesis of prostaglandin E2, the percent of inhibition being more than 90% at the highest dose.

- NO RELEASE. Evidence that compounds (XVIII) and (XII) released nitric oxide after their administration was obtained by measurements of plasma nitrate/nitrite levels, as reported in J. Clin. Invest., 85, 264 (1990). One hour after the administration of either (XVIII) or (XII) compound, the plasma nitrate/nitrite levels had significantly increased by more than 50%. Ketoprofen or Flurbiprofen did not affect plasma nitrate/nitrite levels significantly.

Besides, additional biological studies were performed on derivatives (XII) and (XVIII); said studies have

provided the following results.

GASTROINTESTINAL TOLERABILITY

- RAT GASTRIC MUCOSA INJURY. (XVIII) and (XII) were studied in comparison with the corresponding reference compounds Ketoprofen and Flurbiprofen at doses ranging from 3 to 30 mg/kg p.o., both (XII) and (XVIII) compounds being significantly better tolerated than reference compounds. Ketoprofen or Flurbiprofen caused the onset of gastric damages already at the dose of 3 mg/kg, the severity of such damages being dose-dependent, while (XVIII) or (XII) compounds were well tolerated even at the dose of 30 mg/kg.

The histological evaluation confirmed these findings. Similar differences in the capacity of these compounds to cause gastric and small intestine injury were also observed upon repeated administration of the compounds.

- GASTRIC LEUKOCYTE ADHERENCE/VESSEL DIAMETER. An early event in the pathogenesis of NSAID-induced gastric mucosa injury is the adherence of leukocytes to the endothelium of post-capillary venules, as reported in Gastroenterology 103, 146 (1992); Trends Pharmacol. Sci. 13, 129 (1992); Am.J. Physiol. 262, G903 (1992). Using intravital microscopy, the leucokocyte adherence to mesenteric post-capillary venules could be quantified prior to and during a one hour period after the administration of NSAID. Unlike Ketoprofen or Flurbiprofen, (XVIII) or (XII) did not induce significant

leukocyte adherence, while increasing the diameter of vessels significantly. No changes in blood pressure were observed.

GENERAL PHARMACOLOGY

A secondary pharmacological evaluation of compound (XVIII) or (XII) was performed in comparison with Ketroprofen or Flurbiprofen. No relevant additional adverse reactions were observed affecting the central nervous, autonomic, cardiovascular, respiratory and gastrointestinal systems.

TOXICOLOGY

- ACUTE TOXICOLOGY IN RODENTS.

The acute toxicity of said derivatives (XVIII), (XXIV), (XXV), (XII) and (XXVI) was then evaluated by p.o. administration of a single dose of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), utilizing, for each derivative, groups of 10 Swiss mice. Death incidence and the onset of toxic symptoms were reported for a period of 14 days.

Even after administration of a dose of 100 mg/kg of each compound (XVIII), (XXIV), (XXV), (XII) and (XXVI), no apparent toxicity symptoms were noticed in the animals studied.

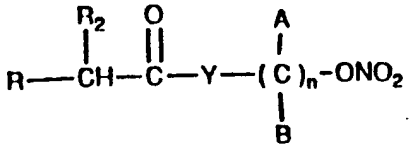
In particular, preliminary studies on compounds (XVIII) or (XII) were performed in the mouse by two administration routes. No evident toxicity was observed in the animals treated with oral or intraperitoneal doses of

300 mg/kg of either compound.

- MAXIMUM TOLERATED DOSE IN NON RODENTS. Preliminary studies indicate that compounds (XVIII) and (XII) were very well tolerated in this animal species that is known to be particularly sensitive to this class of compounds. The animals were administered increasing oral doses up to 30 mg/kg of either compound and no apparent symptoms were observed, while the reference compounds Ketoprofen and Flurbiprofen, administred at the dose of 10 mg/kg caused the death of the animals.

CLAIMS

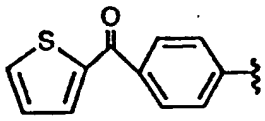
1. Nitric esters characterized in that they have the following general formula:



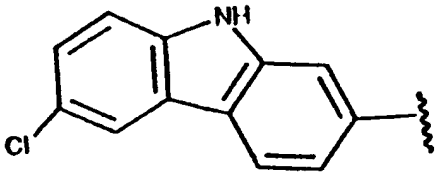
(I)

where:

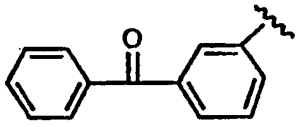
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



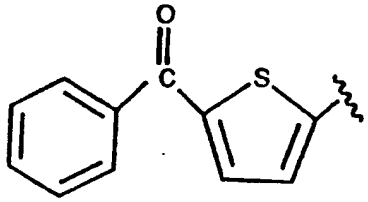
(II)



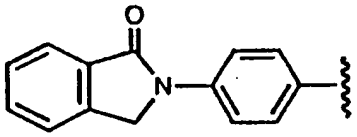
(XXI)



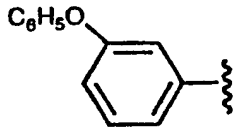
(IV)



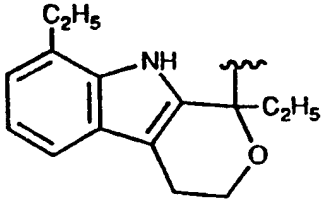
(XXXV)



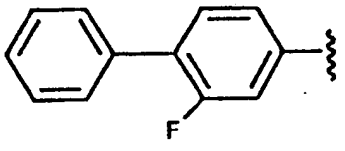
(VI)



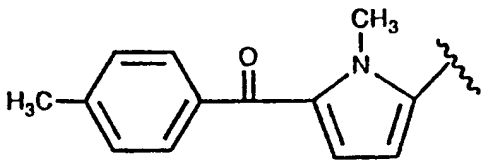
(VII)



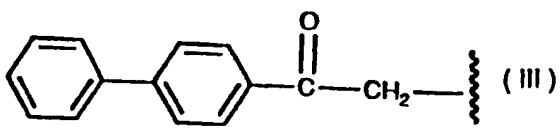
(VIII)



(IX)



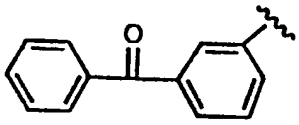
(X)



(III)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10.

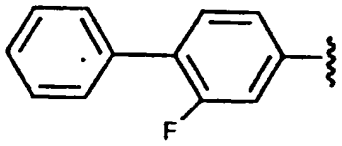
2. Nitric ester according to claim 1, characterized in that R is:



(IV)

R_2 is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen and n is equal to four.

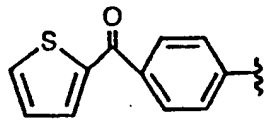
3. Nitric ester according to claim 1, characterized in that R is equal to:



(IX)

R_2 is equal to methyl, Y is equal to oxygen, A and B are equal to hydrogen and n is equal to four.

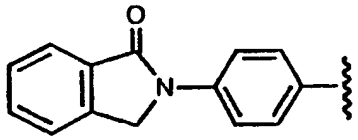
4. Nitric ester according to claim 1, characterized in that R is equal to:



(II)

R_2 is equal to methyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

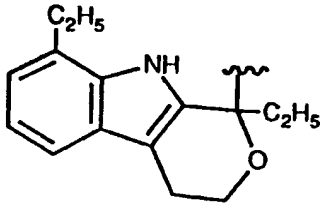
5. Nitric ester according to claim 1, characterized in that R is equal to:



(VI)

R_2 is equal to ethyl, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

6. Nitric ester according to claim 1, characterized in that R is equal to:



(VIII)

R_2 is equal to hydrogen, A and B are equal to hydrogen, Y is equal to oxygen, and n is equal to four.

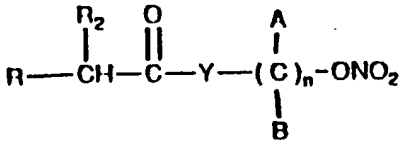
7. Nitric esters according to claim 1, characterized in that they are utilizable in pharmaceutics as anti-

inflammatory agents.

8. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of rheumatic diseases, disorders of immunologic nature, and slight-middle severity painful conditions.

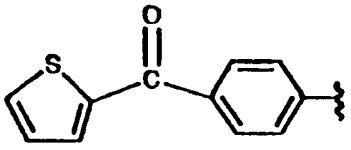
9. Nitric esters according to claim 1, characterized in that they are utilizable in the treatment of diseases affecting the cardiovascular system, the treatment of miocardial and brain ischemiae and in cases of arterial thromobosis as platelet anti-aggregation agents.

10. Process for the preparation of nitric esters according to claim 1 and having the following general formula:

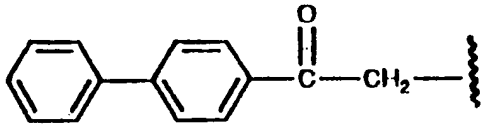


(I)

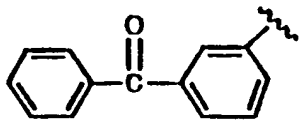
where A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R is chosen among:



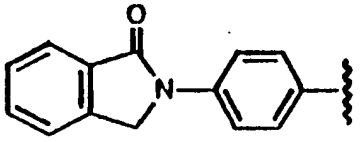
(II)



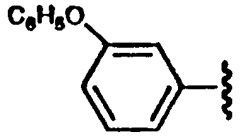
(III)



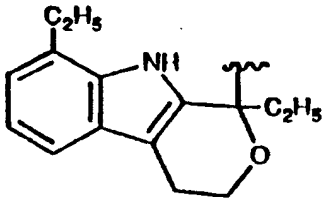
(IV)



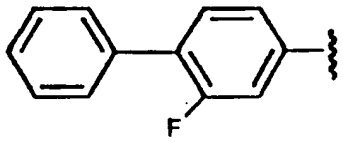
(VI)



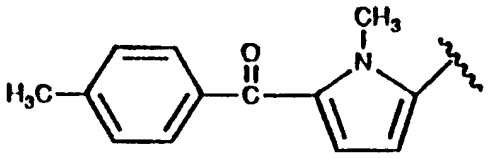
(VII)



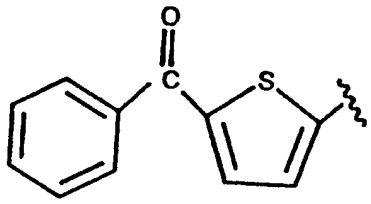
(VIII)



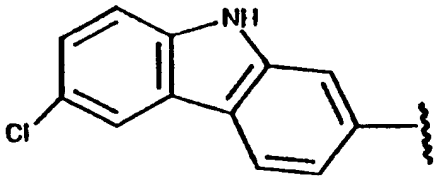
(IX)



(X)



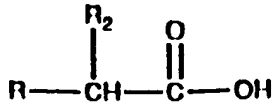
(XXXV)



(XXI)

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl chain, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:

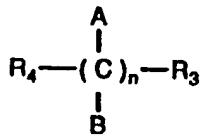


(XIV)

where R is chosen among the following structures: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV),

or preparation of derivatives (XIV) functionalized to the carboxylic group as acilic chlorides, anhydrides or the like;

- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:



(XV)

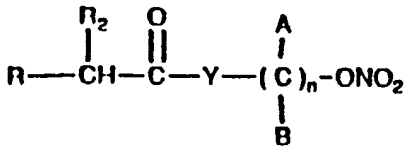
where:

R_4 is chosen among chlorine, bromine, NHR_6, with R_6 hydrogen linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted

or non substituted alkyl chains, R_3 is chosen among chlorine, bromine and iodine, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

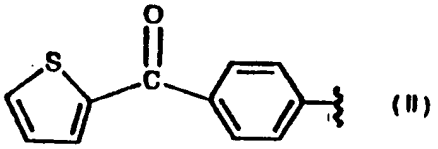
11. Process for the preparation of nitric esters according to claim 1 and having the following general formula:



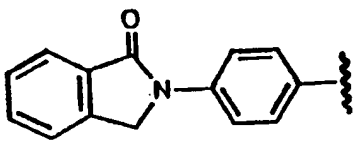
(I)

where:

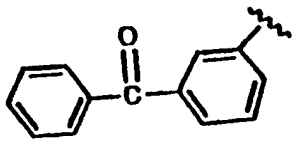
A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, R is chosen among:



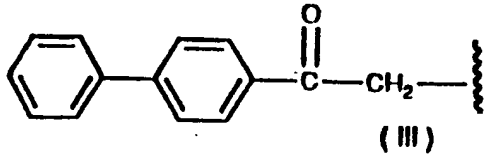
(II)



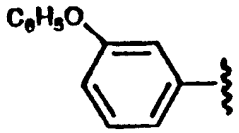
(VI)



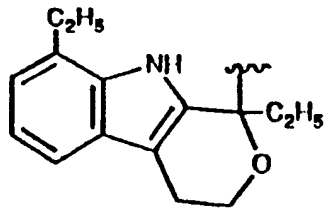
(IV)



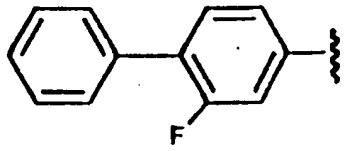
(III)



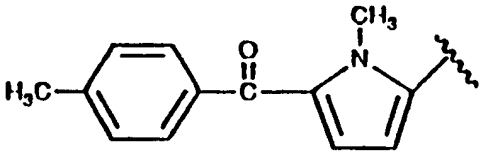
(VII)



(VIII)

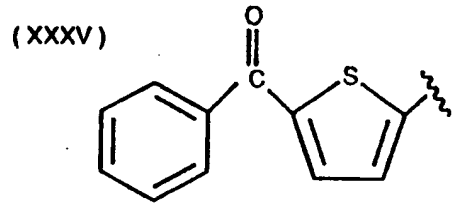


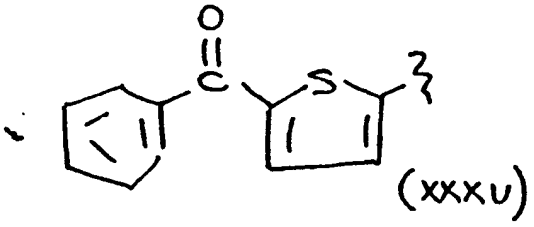
(IX)



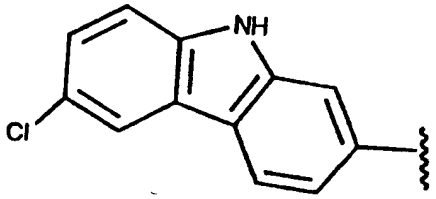
(X)

(XXXV)





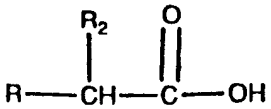
(XXXV)



(XXI)

Y is chosen among oxygen, NH, NR_1, where R_1 is a linear or branched alkyl group, and n is comprised between 1 and 10, characterized in that it comprises the following steps:

- Preparation of sodium salt of derivatives having the following general formula:

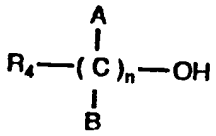


(XIV)

where R is chosen among the following structures: (II), (III), (IV), (VI), (VII), (VIII), (IX), (X), (XXI), (XXXV),

R_2 is chosen among hydrogen, methyl, ethyl, alkyl chains linear or branched by 3 to 12 carbon atoms, substituted or non substituted, or preparation of derivatives (XIV) functionalized to the caboxylic group, such as acilic chlorides, anhydrides and the like;

- Reaction between the sodium salt of said derivatives (XIV) or of said derivatives (XIV) functionalized to the carboxylic group, with a compound having the following general formula:



(XVI)

where:

R_4 is chosen among chlorine, bromine, NHR_6, with R_6 hydrogen, linear or branched alkyl chain, A and B are chosen among hydrogen, linear or branched, substituted or non substituted alkyl chains, and n is comprised between 1 and 10, obtaining the relative monomeric esters or the relative amides;

- Reaction of said monomeric esters or said amides with an halogenating compound such as PBr_3 or the like, obtaining said monomeric esters or said amides, characterized by the presence of a terminal halogen group;

- Reaction of said monomeric esters or said amides characterized by the presence of a terminal halogen group with a nitrating agent such as $AgNO_3$ or the like, obtaining nitric esters of derivatives (I).

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 93/03193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C203/04 A61K31/21 C07D333/22 C07D209/46 C07D491/04
A61K31/40 A61K31/38 C07D207/337 C07D209/88 C07D333/24
A61K31/16 C07C235/78 C07C235/34 C07C233/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 359 335 (CEDONA PHARMACEUTICALS B.V.) 21 March 1990 see page 4; claims	1,9
A	WO,A,92 01668 (ITALFARMACO S.P.A.) 6 February 1992 see claims	1,9
A	EP,A,0 300 400 (FUJISAWA PHARMACEUTICAL CO., LTD.) 25 January 1989 see claims	1,9
A	US,A,4 585 877 (C.A. DEMERSON ET AL.) 29 April 1986 see example 4	1,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1994	16. 02. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bonnevalle, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 93/03193

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 988 728 (S.H.GERSON ET AL.) 29 January 1991 see the whole document	1,7
A	FR,A,2 612 185 (FARMITALIA CARLO ERBA S.R.L.) 16 September 1988 see page 12; claims	1,7,9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 93/03193

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0359335	21-03-90	NL-A-	8802276	02-04-90
		AU-B-	638413	01-07-93
		AU-A-	4133089	22-03-90
		JP-A-	2134316	23-05-90
		US-A-	5049694	17-09-91
WO-A-9201668	06-02-92	AU-A-	8097491	18-02-92
		EP-A-	0540544	12-05-93
EP-A-0300400	25-01-89	AU-B-	623858	28-05-92
		AU-A-	1919988	27-01-89
		JP-C-	1666528	29-05-92
		JP-A-	2028167	30-01-90
		JP-B-	3031709	08-05-91
		SU-A-	1706388	15-01-92
		SU-A-	1760984	07-09-92
		US-A-	4923886	08-05-90
		US-A-	5010093	23-04-91
US-A-4585877	29-04-86	NONE		
US-A-4988728	29-01-91	NONE		
FR-A-2612185	16-09-88	AT-B-	392068	25-01-91
		AU-B-	605253	10-01-91
		AU-A-	1267988	08-09-88
		BE-A-	1003280	18-02-92
		CH-A-	675419	28-09-90
		DE-A-	3807595	22-09-88
		GB-A,B	2204579	16-11-88
		JP-A-	63238058	04-10-88
		NL-A-	8800575	03-10-88
		SE-A-	8800846	11-09-88

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07C 203/04, 327/34, C07D 209/28, 233/64, 495/04, C07C 211/49, C07F 9/38, C07D 295/088, 207/16, 499/32, 473/08, C07C 211/42, C07D 219/10, 307/30, 401/14, 401/12, 407/04, 417/12, C07H 15/252, A61K 31/21

A2

(11) International Publication Number: WO 00/61537

(43) International Publication Date: 19 October 2000 (19.10.00)

(21) International Application Number: PCT/EP00/03234

(22) International Filing Date: 11 April 2000 (11.04.00)

(30) Priority Data:
MI99A000753 13 April 1999 (13.04.99) IT

(71) Applicant *(for all designated States except US)*: NICOX S.A. [FR/FR]; 45 Avenue Kléber, F–75116 Paris (FR).

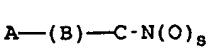
(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I–20052 Monza (IT).

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I–20129 Milano (IT).

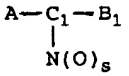
(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: PHARMACEUTICAL COMPOUNDS



(I)



(II)

(57) Abstract

Compounds or their salts having general formulas (I) and (II): wherein s is and integer equal to 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacological tests reported in the description, C and C_1 are two bivalent radicals. The precursors of the radicals B and B_1 are such as to meet the pharmacological test reported in the description.